

Marcus Gastreich

Link, Merge & Grow Fragments Interactively

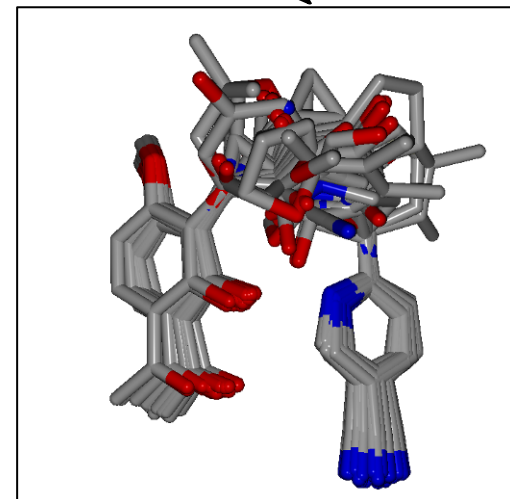
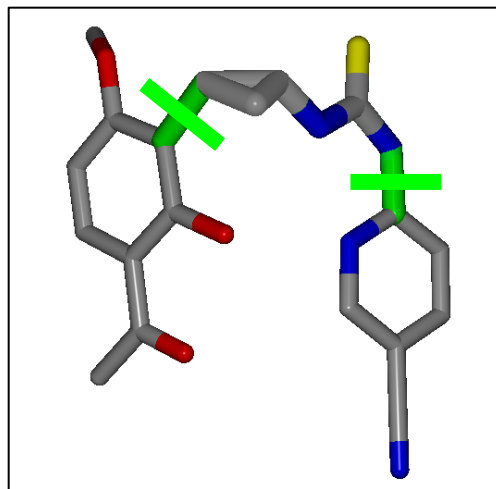
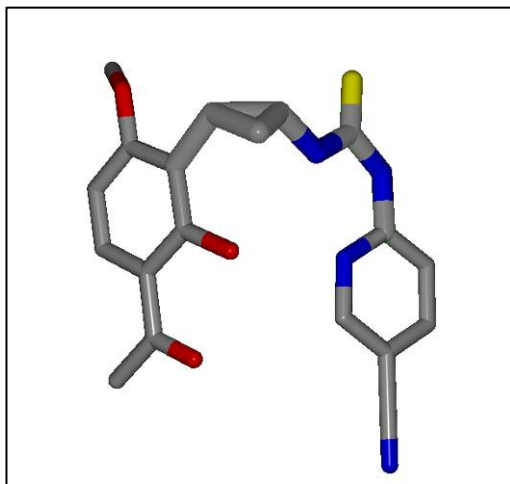
Roche 2007: Re-Scaffolding Using Vectors



define "Exit Vectors"



search 3D fragment library



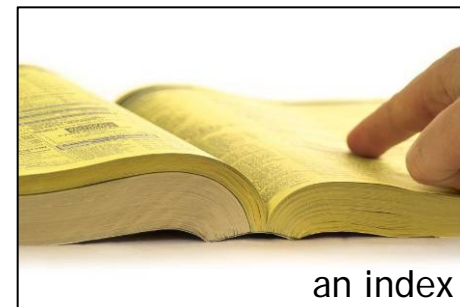
=> **ReCore**. Software development by Maass, Rarey (ZBH, Hamburg) and Roche



Maaß, Schulz-Gasch, Stahl Rarey, *J. Chem. Inf. Mod.*, **47**, 390-399 (2007)

ReCore: Indexed Searching

- ReCore has an “index” to search extremely fast: instead of looking at every single possibility, you jump to the answer in seconds:

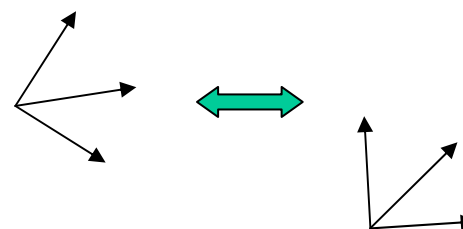


- The Index needs a pre-generated “descriptor”:

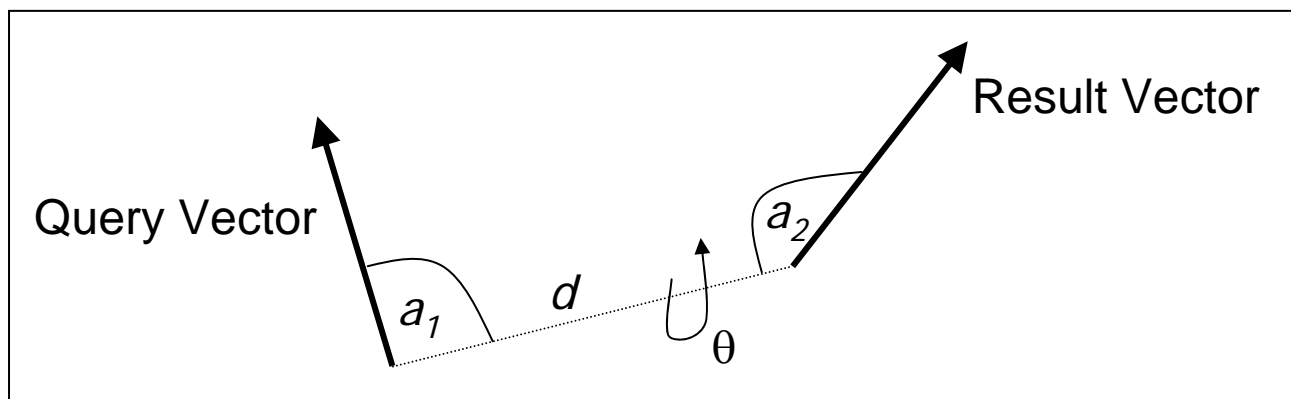
telephone book:the alphabet



ReCore: Vector relationships



- purely geometric (CAVEAT*-like)



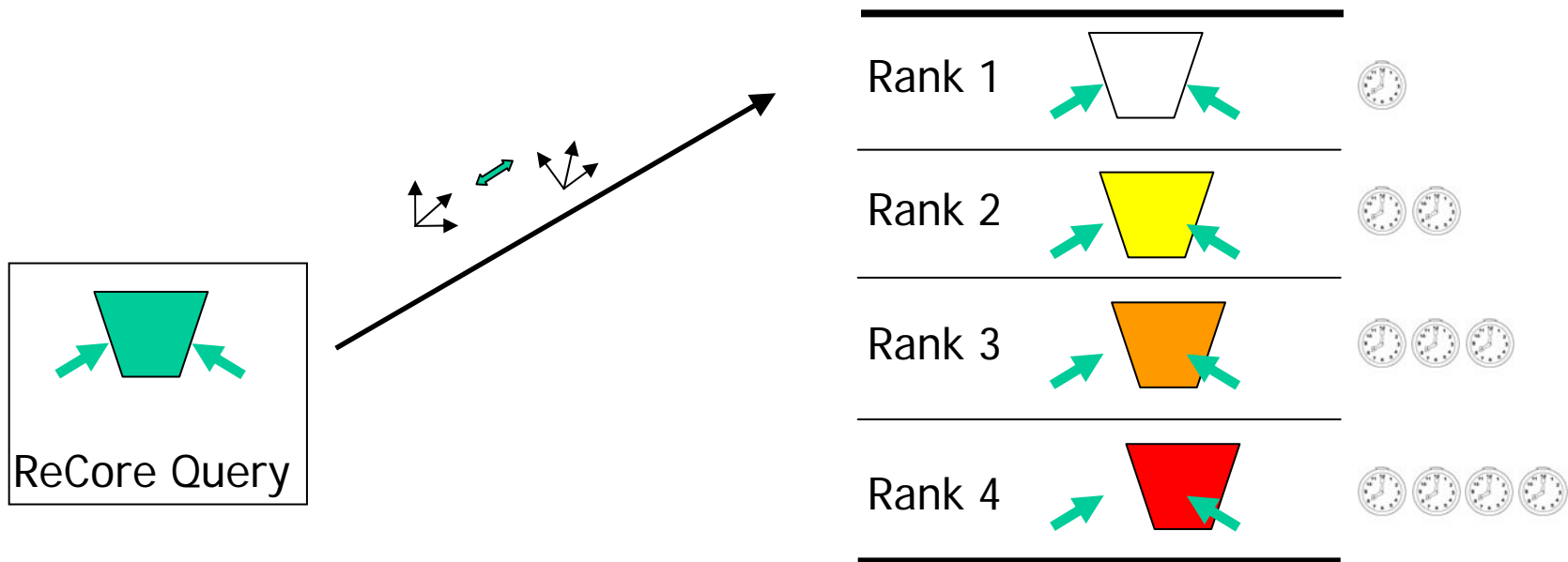
- according to Euclidean distance in 4D:
 - distance d
 - torsion θ
 - 2x angles a_1 and a_2 formed with connecting path

In other words: The better the geometric fit, the better the rank

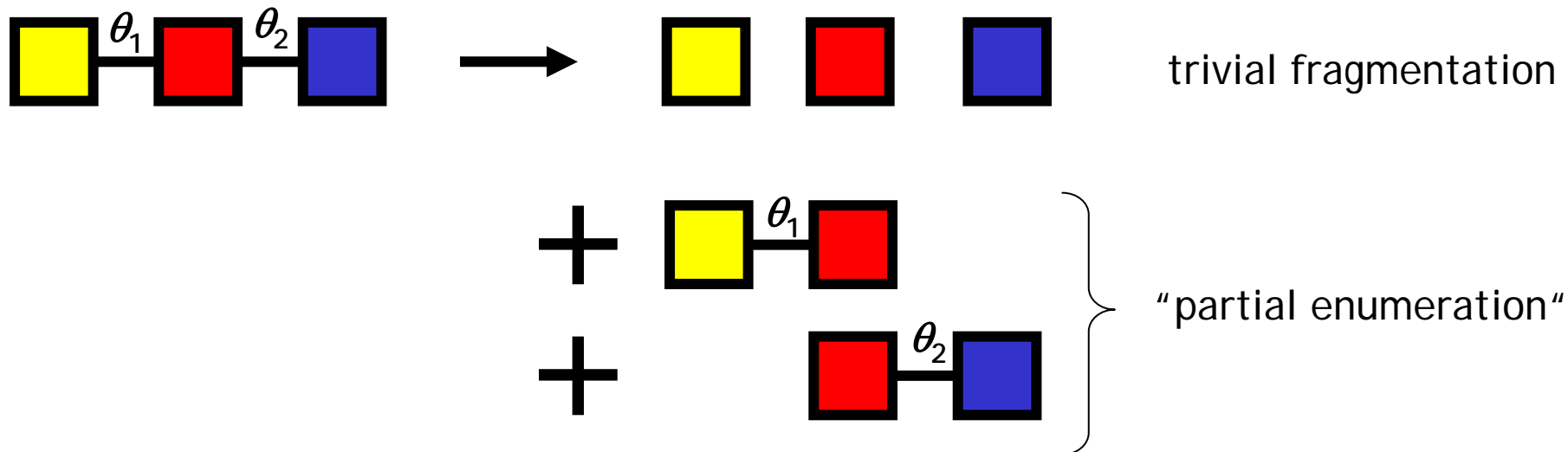
* Lauri & Bartlett, *JCAMD*, **8**, 51-66 (1994)

ReCore: Results Delivery

- By design the best fitting replacements are found first
- The ranking is according to deviation from perfect vector overlap



A ReCore Specialty: "3D Shredding"

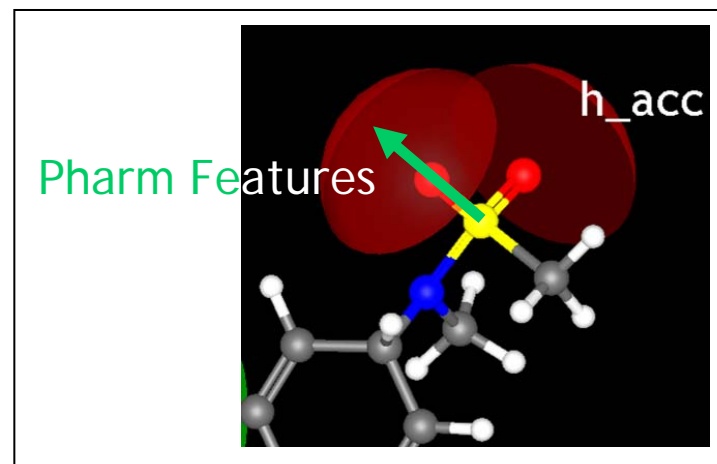
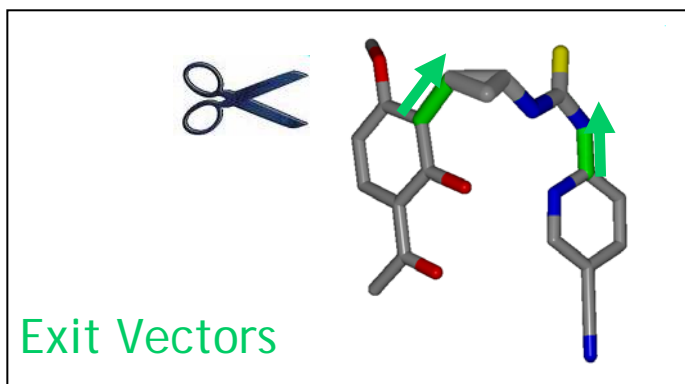


Advantages:

- more possibilities
- bridging larger gaps
- still respect conformation/torsions seen in root structure (ideally: experiment/bioactive)

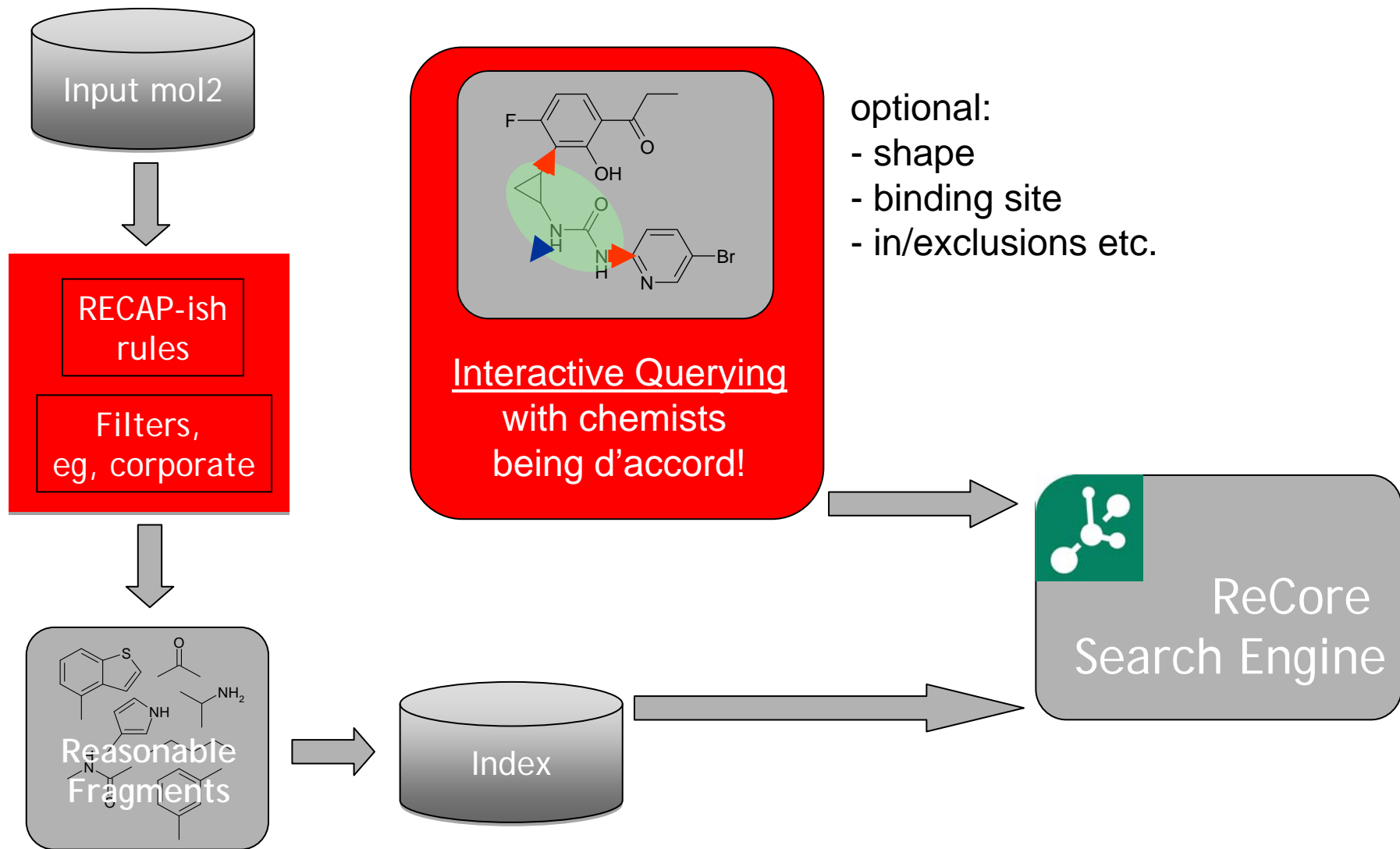
ReCore Needs at least 2 Vectors

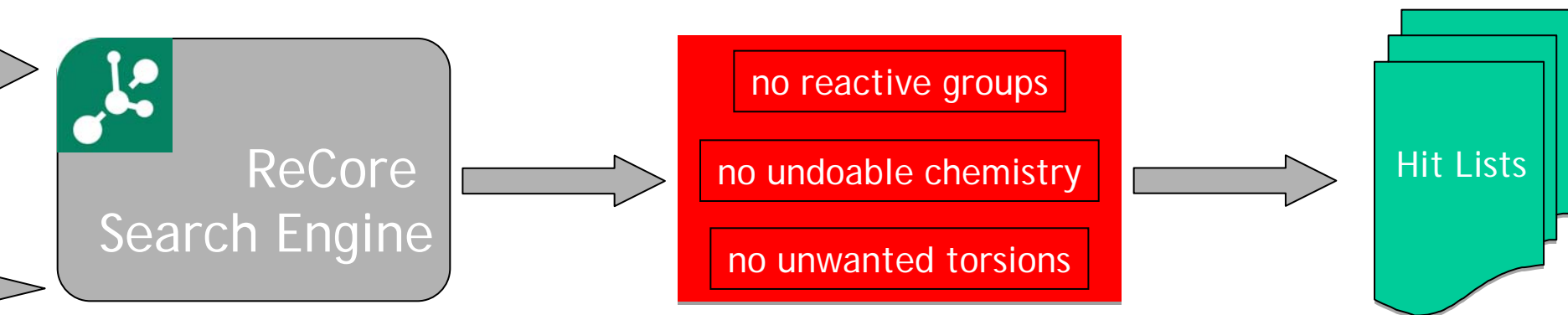
- Vectors = EVs and Pharm Features (non-spherical pharmacophores):



⇒ Sensible Query Scenarios:

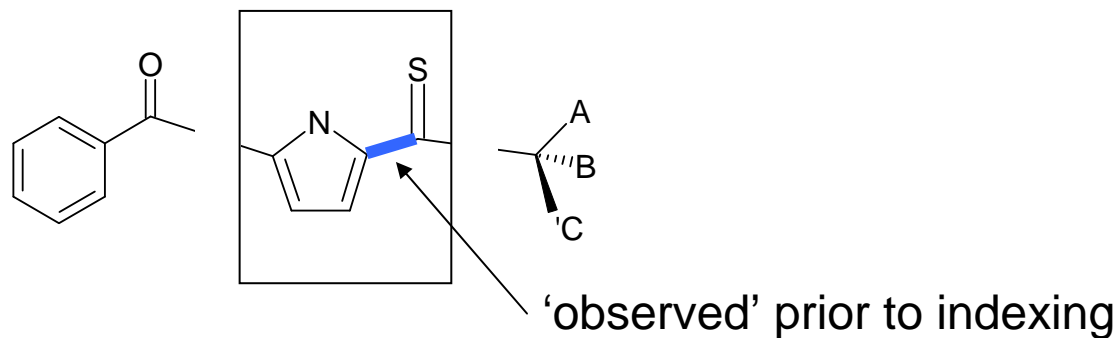
- 2 EV
- 1 EV + 1 **directed** Pharm Feature
- + opt'l: any Pharm Features or EVs
- + opt'l: any Pharm Features



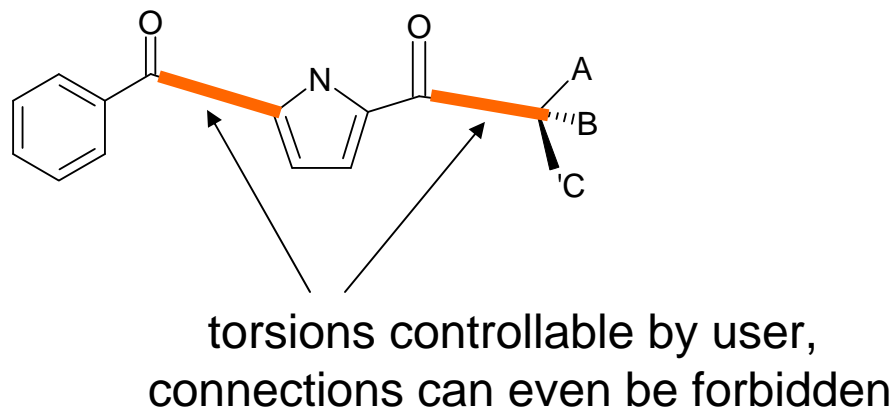


Avoiding Bogus Conformations

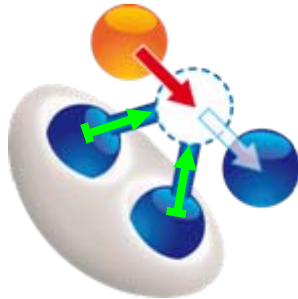
1. Torsions within the fragment (typically from expt., or from Corina or the like)



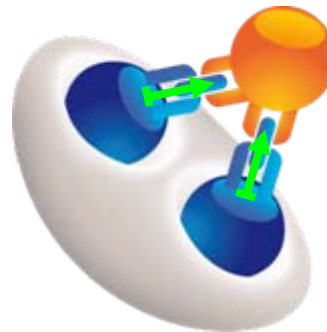
2. Torsions upon forming new single bonds: Link Constraints



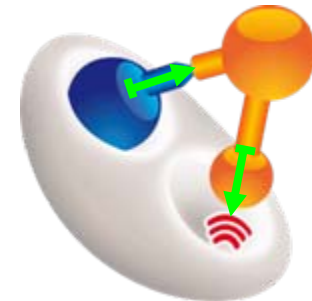
A Striking Analogy



Core Replacement

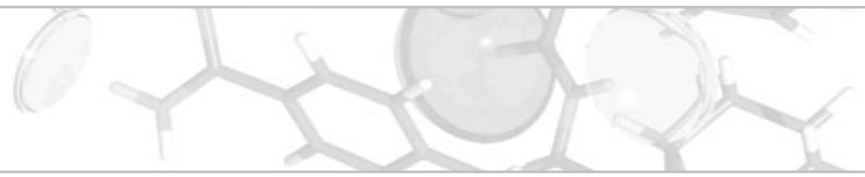


Merging & Linking



Growing

Essentially, this required dealing with multiple input molecules.
All we need is 2 VECTORS.

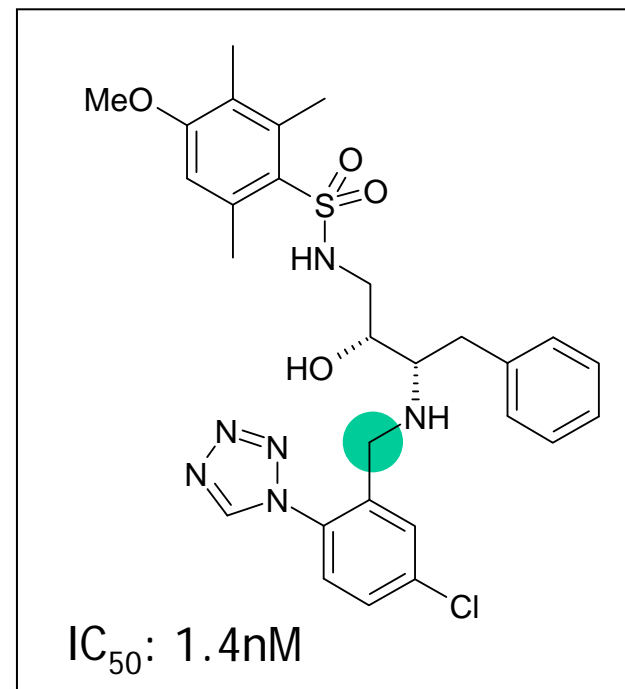
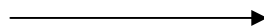
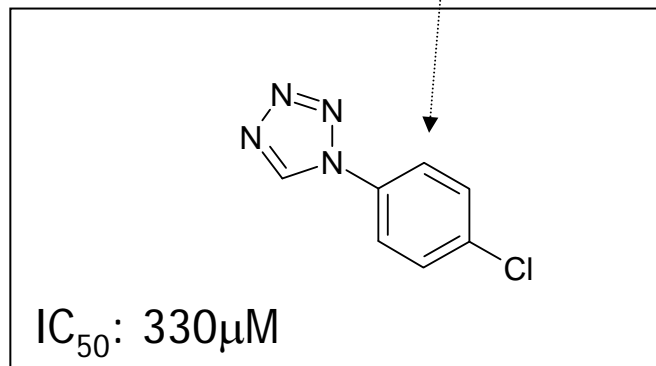
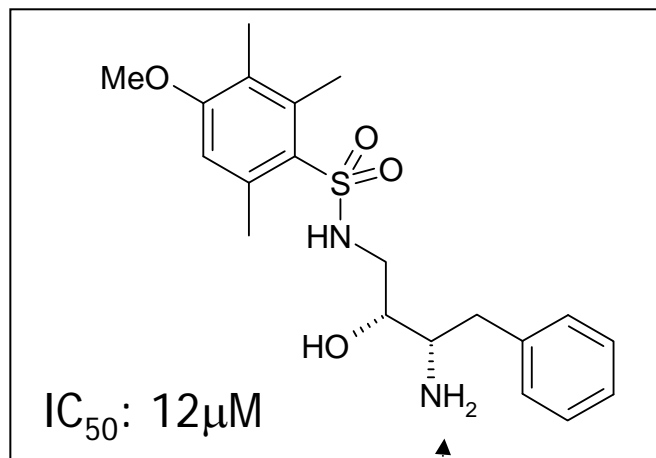


Linking / Merging: Examples



Fragment Linking - A First, Simple Example

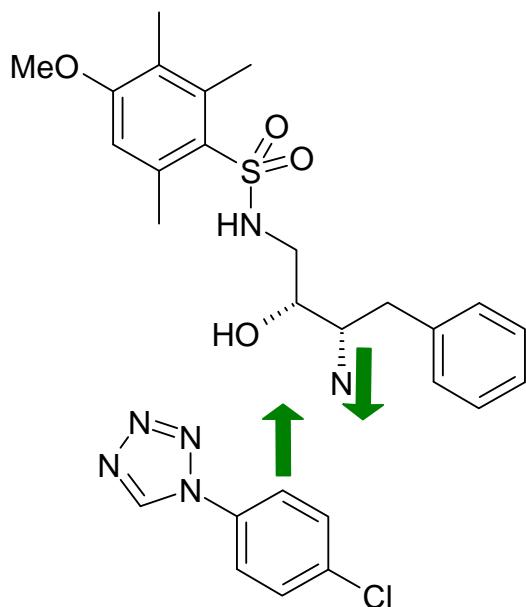
How close do we get to Howard et al.'s JMC success with Thrombin?



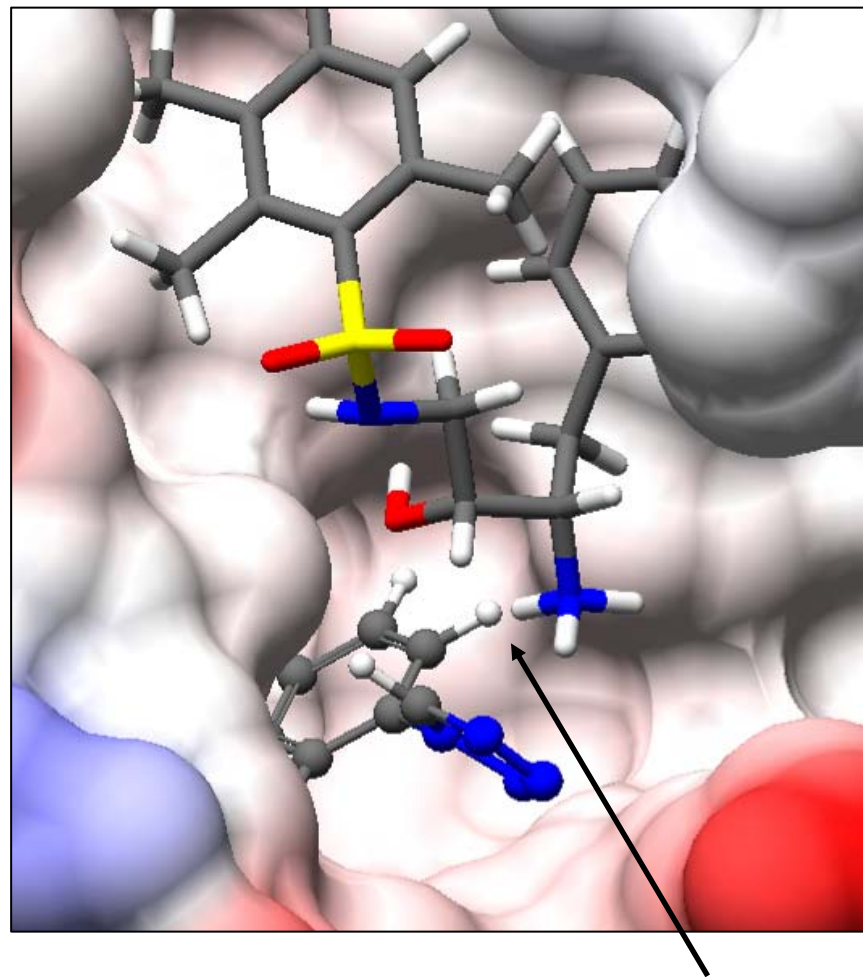
Howard et al., JMC 49 1346 (2006)

Fragment Linking - A First, Simple Example

ReCore Queries with alignment of ligand PDBs 2c93 and 2c90:

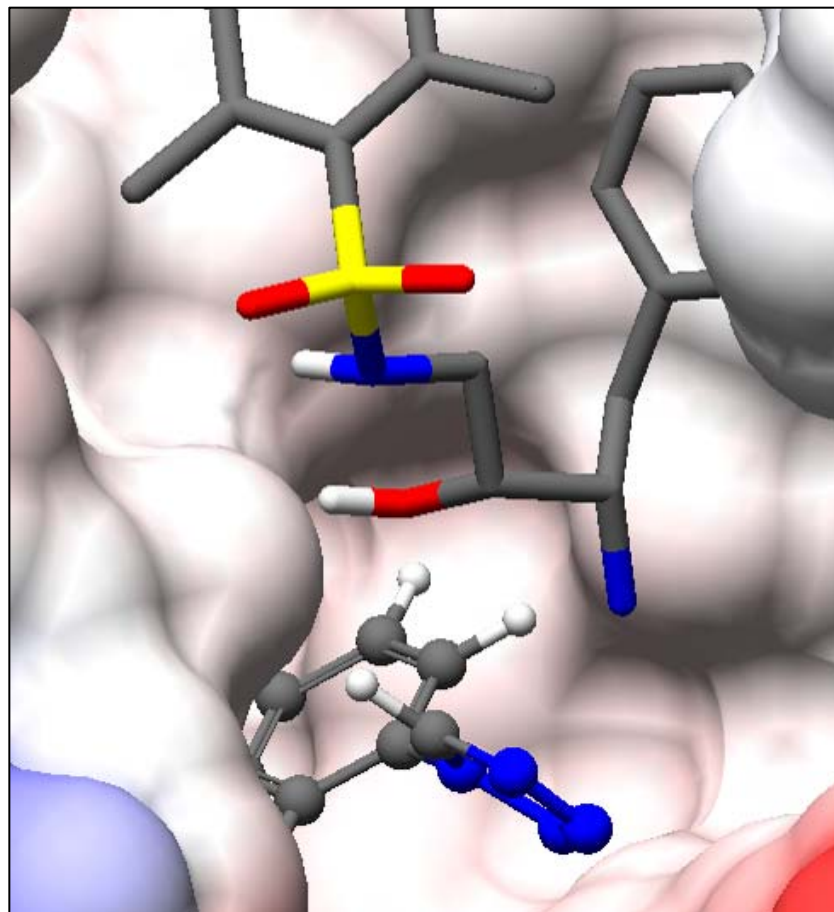
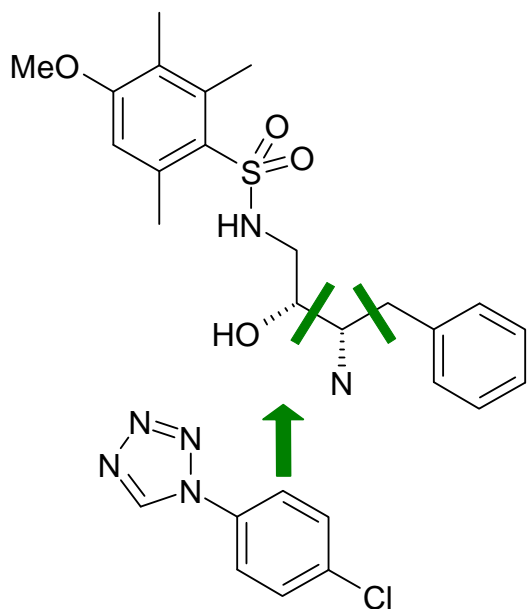


This is too easy! Roche do not have simple $-CH_n-$ as linkers, so we don't either...



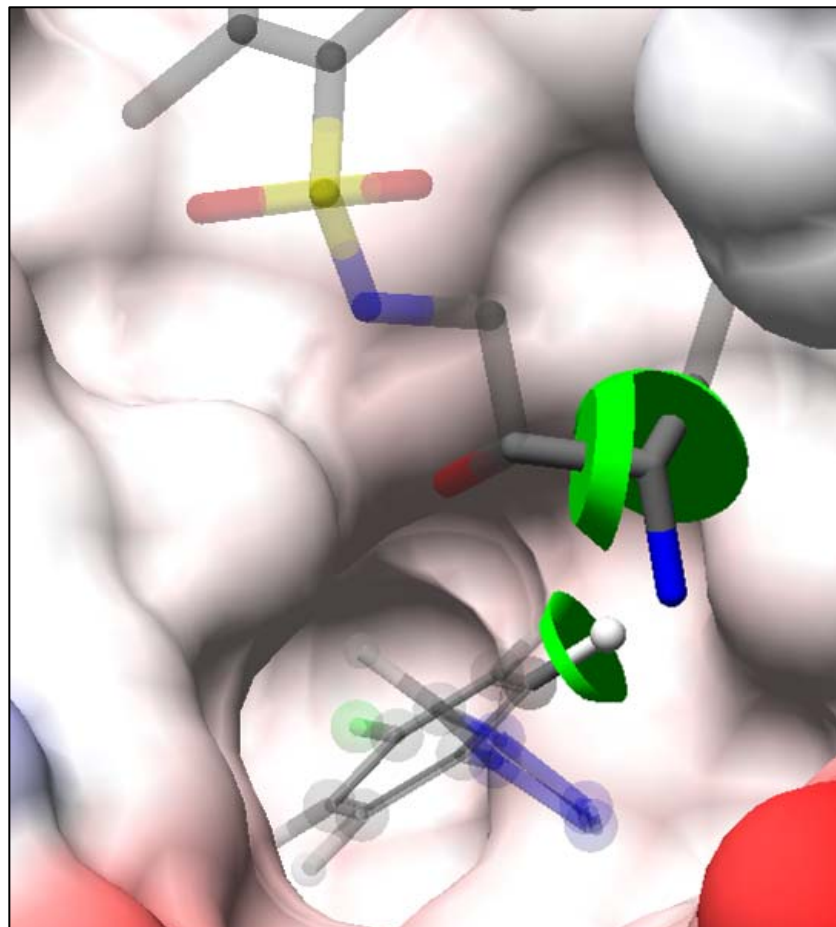
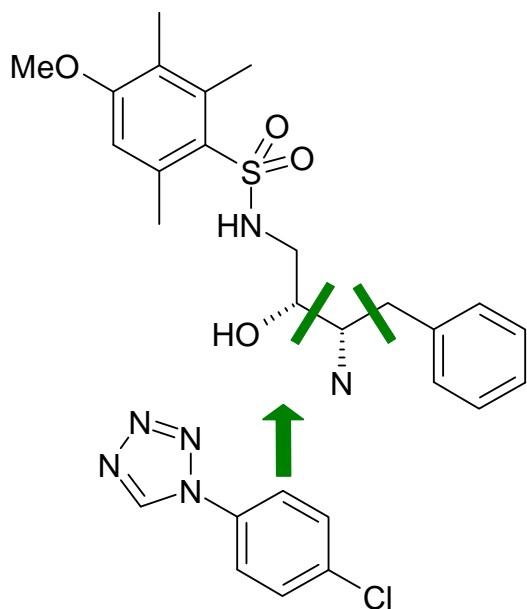
Fragment Linking - A First, Simple Example

Can we 'carve out' the amine? And still link to the chlorophenyl?



Fragment Linking - A First, Simple Example

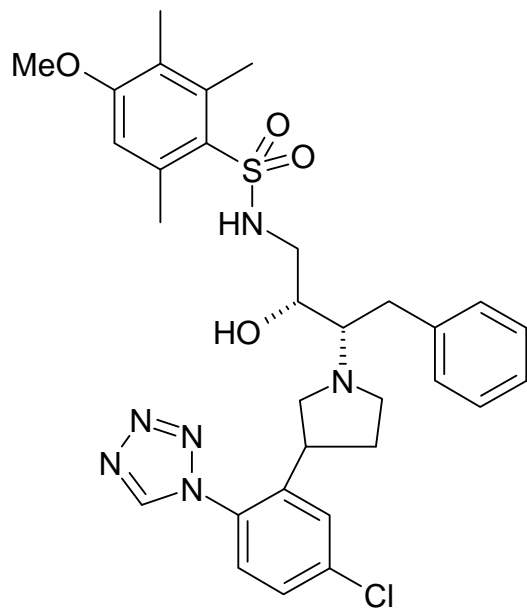
Can we 'carve out' the amine? And still link to the chlorophenyl?



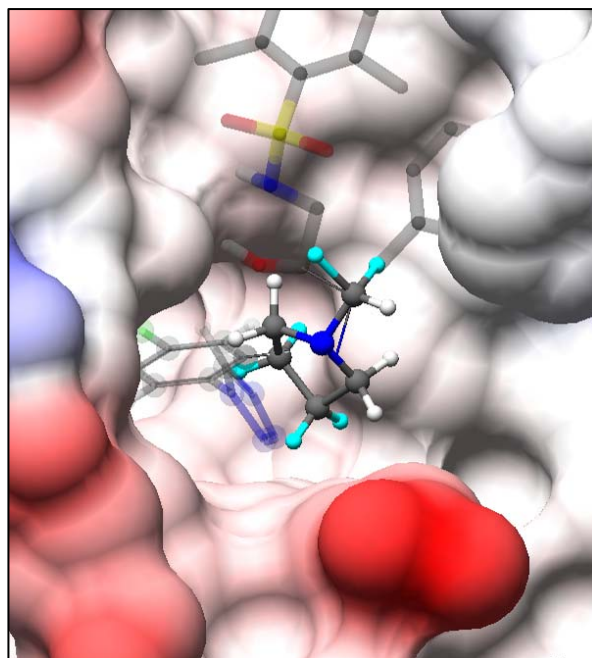
Fragment Linking - A First, Simple Example

Yes, that's possible:

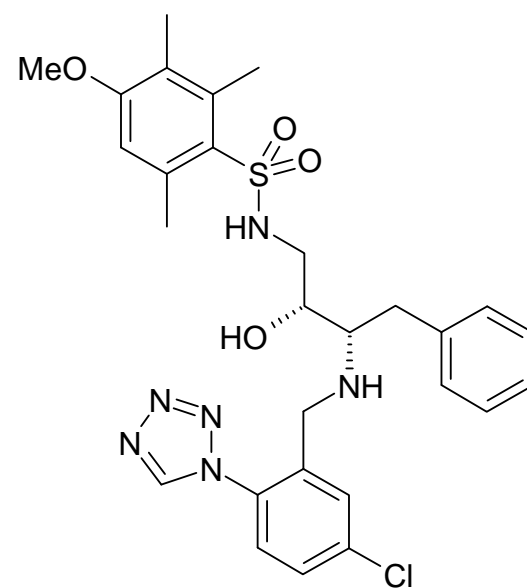
Found first (= Rank 1):



IC₅₀: ??



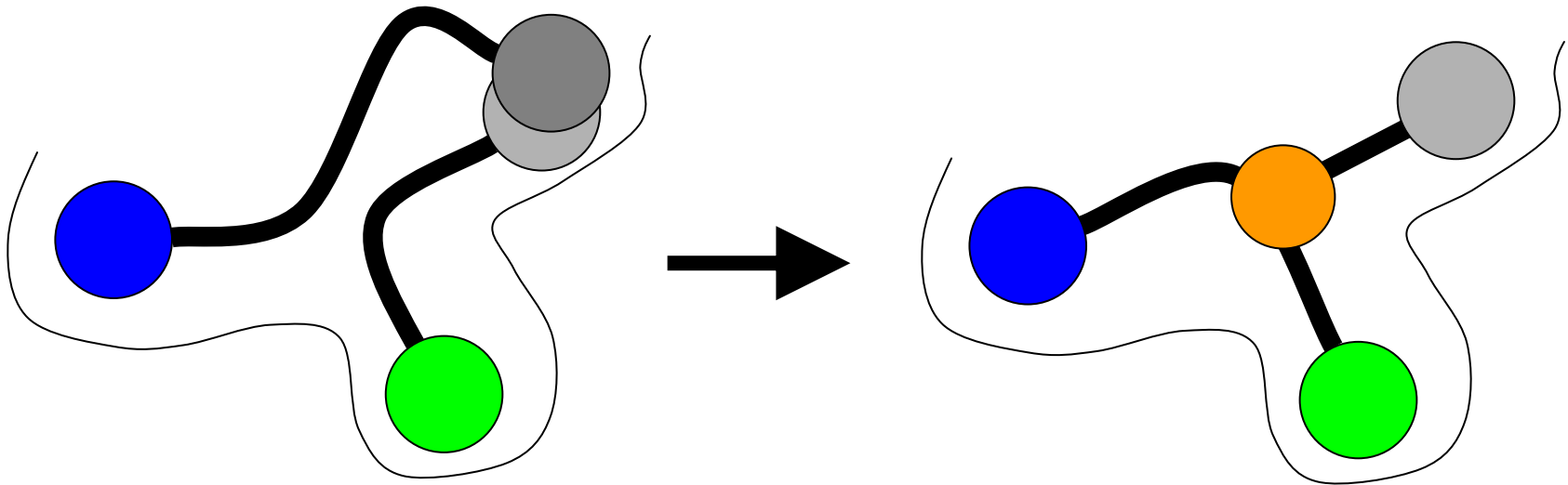
published structure:



IC₅₀: 1.4nM

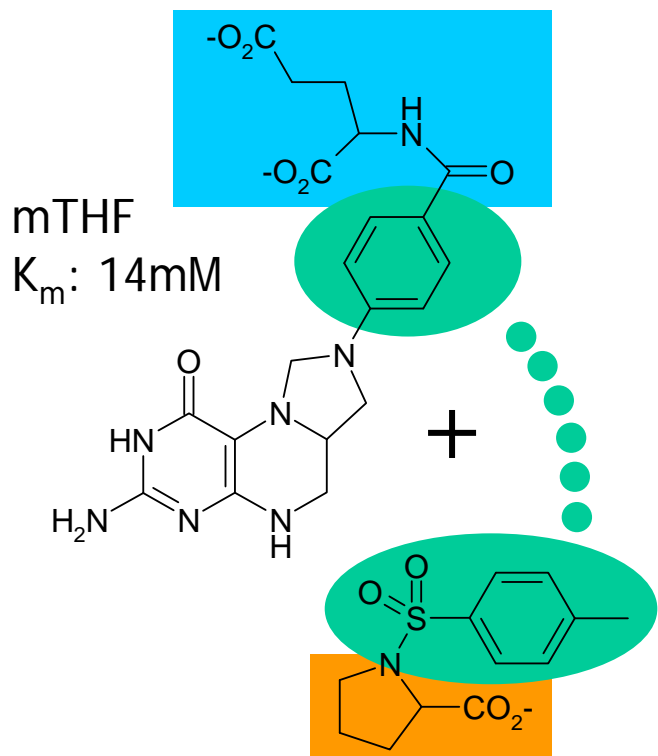
... and: Fragment Merging

The idea: Connect multiple known fragment binders where they overlap.



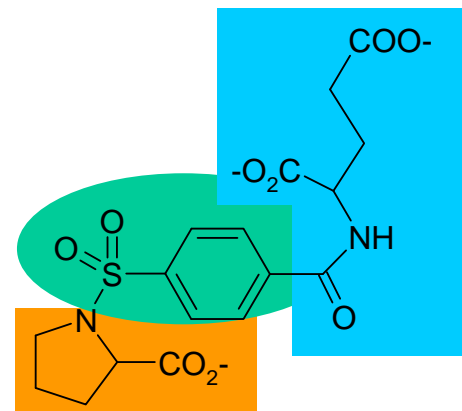
A Tough Merging Example

Thymidylate Synthase Inhibition à la Sunesis (Erlanson et al., PNAS 2000 97 9367)



PDB: 1F4E
K_i: 1.1mM

"...tosyl group is in roughly the same position and orientation as the benzamide moiety of methylenetetrahydrofolate..."

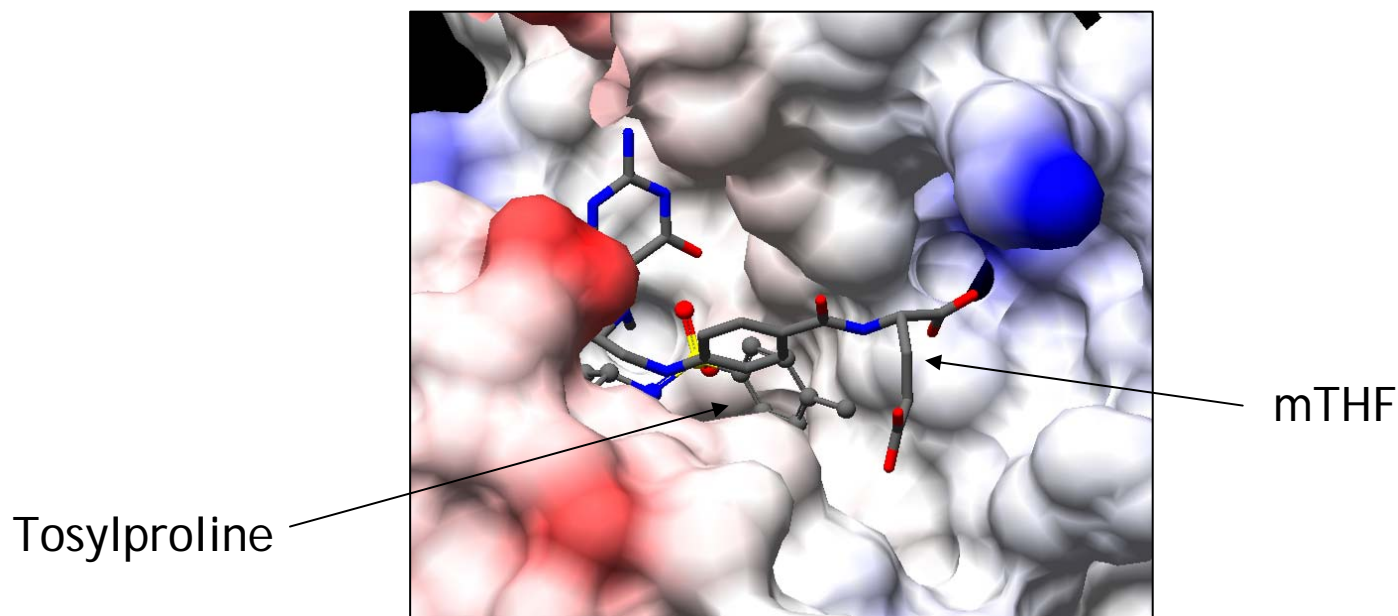


24μM,
further opt'd to 330nM

A Tough Merging Example

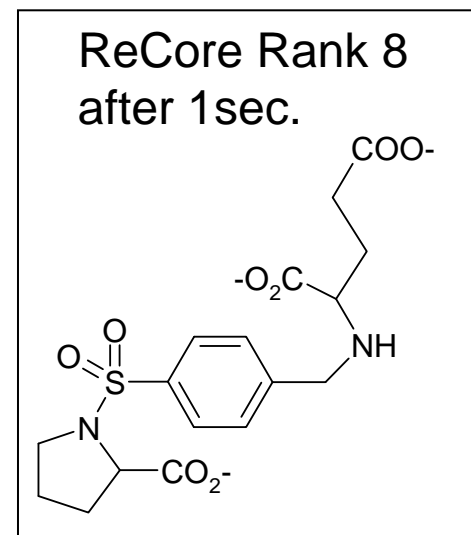
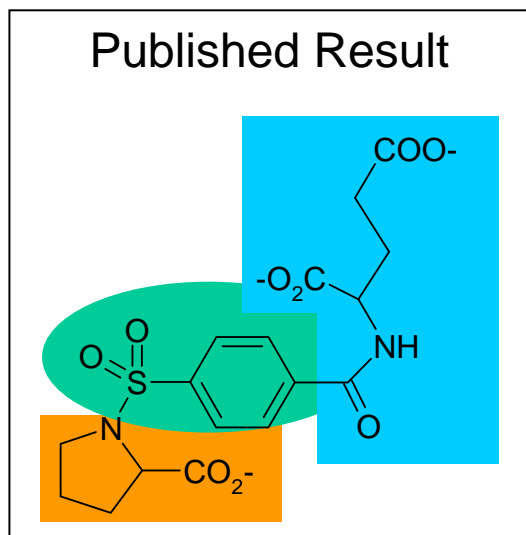
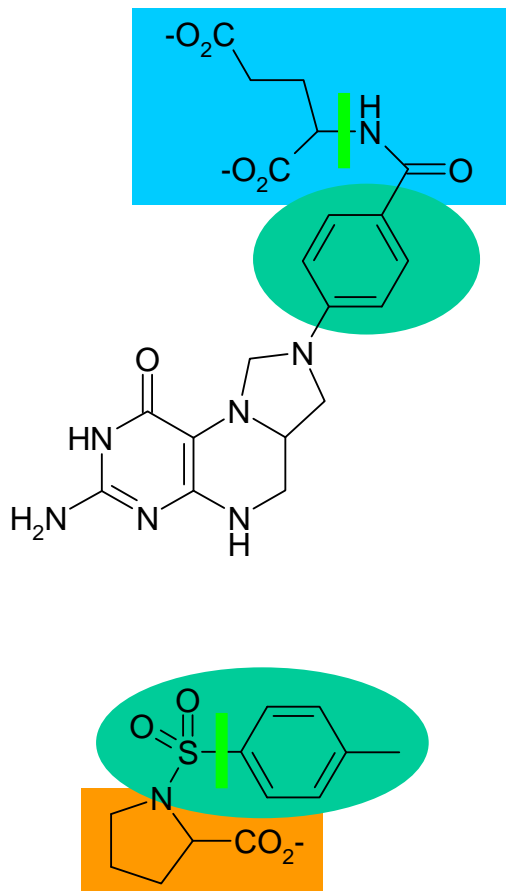
Thymidylate Synthase Inhibition à la Sunesis (Erlanson et al., PNAS 2000 97 9367)

"...tosyl group is in roughly the same position and orientation as the benzamide moiety of methylenetetrahydrofolate..."



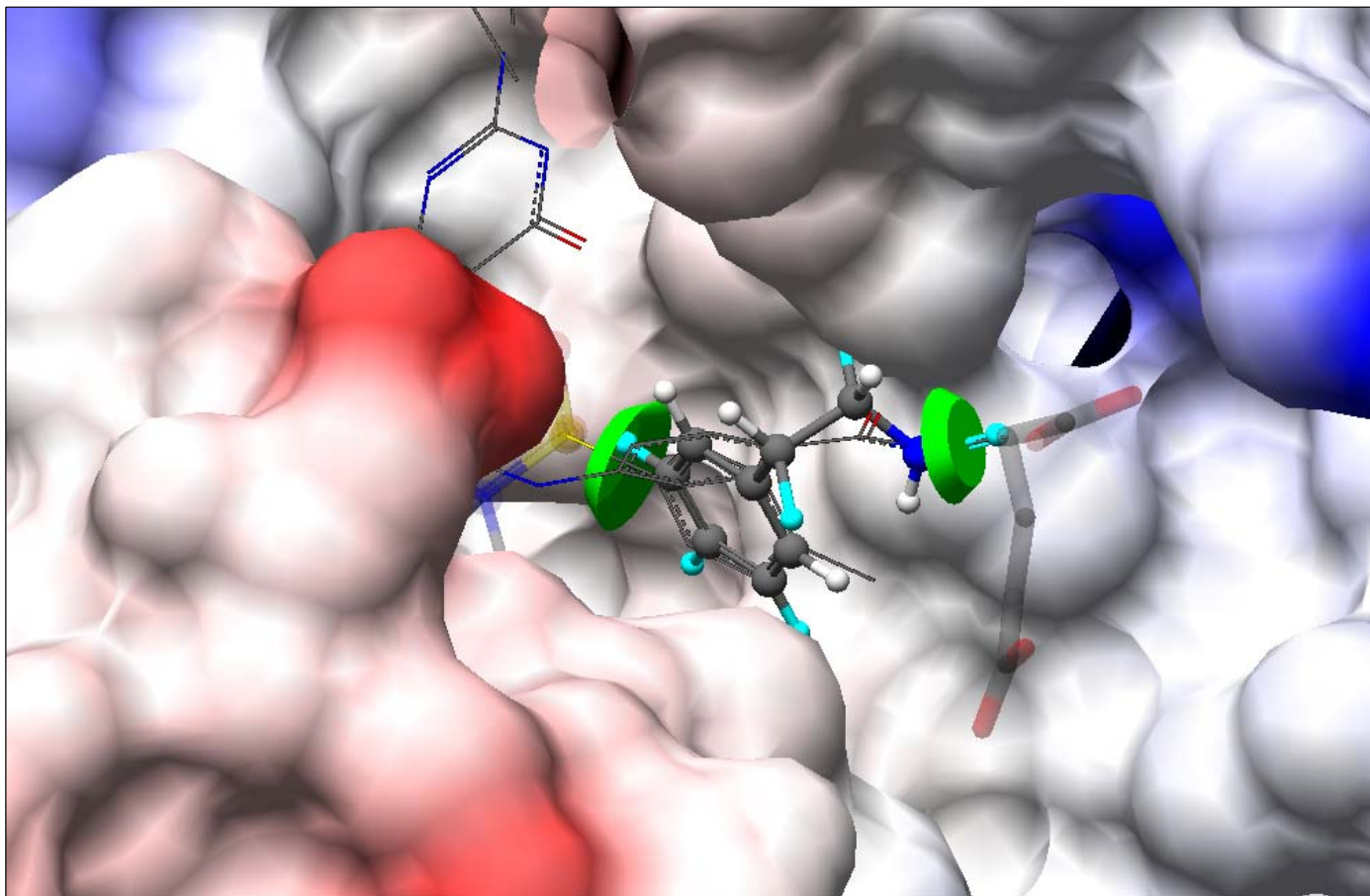
A Tough Merging Example

Thymidylate Synthase Inhibition à la Sunesis (Erlanson et al., PNAS 2000 97 9367)



To ensure the result accommodates in the pocket the input ligand envelope shapes were used.

A Tough Merging Example

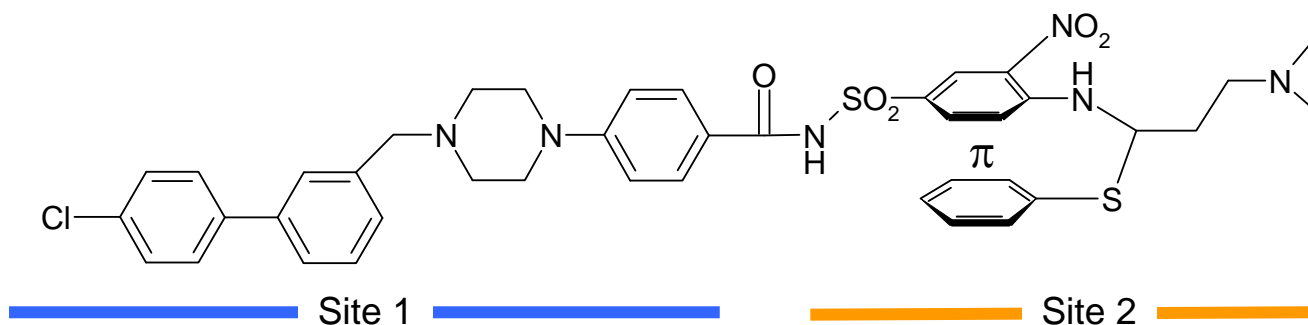




Growing into a π - π Interaction Pattern

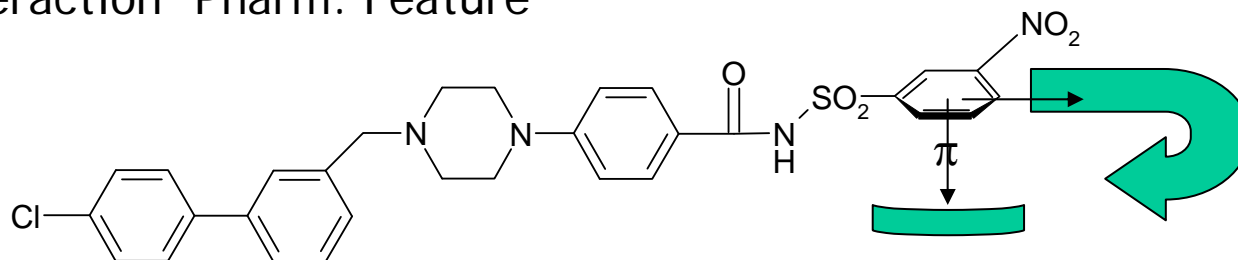
Bcl-2 protein example from Abbott (Oltersdorf et al, Nature 435 (2005) 677).

Let us try to get the π -stacking right as in the original finding in ABT-737



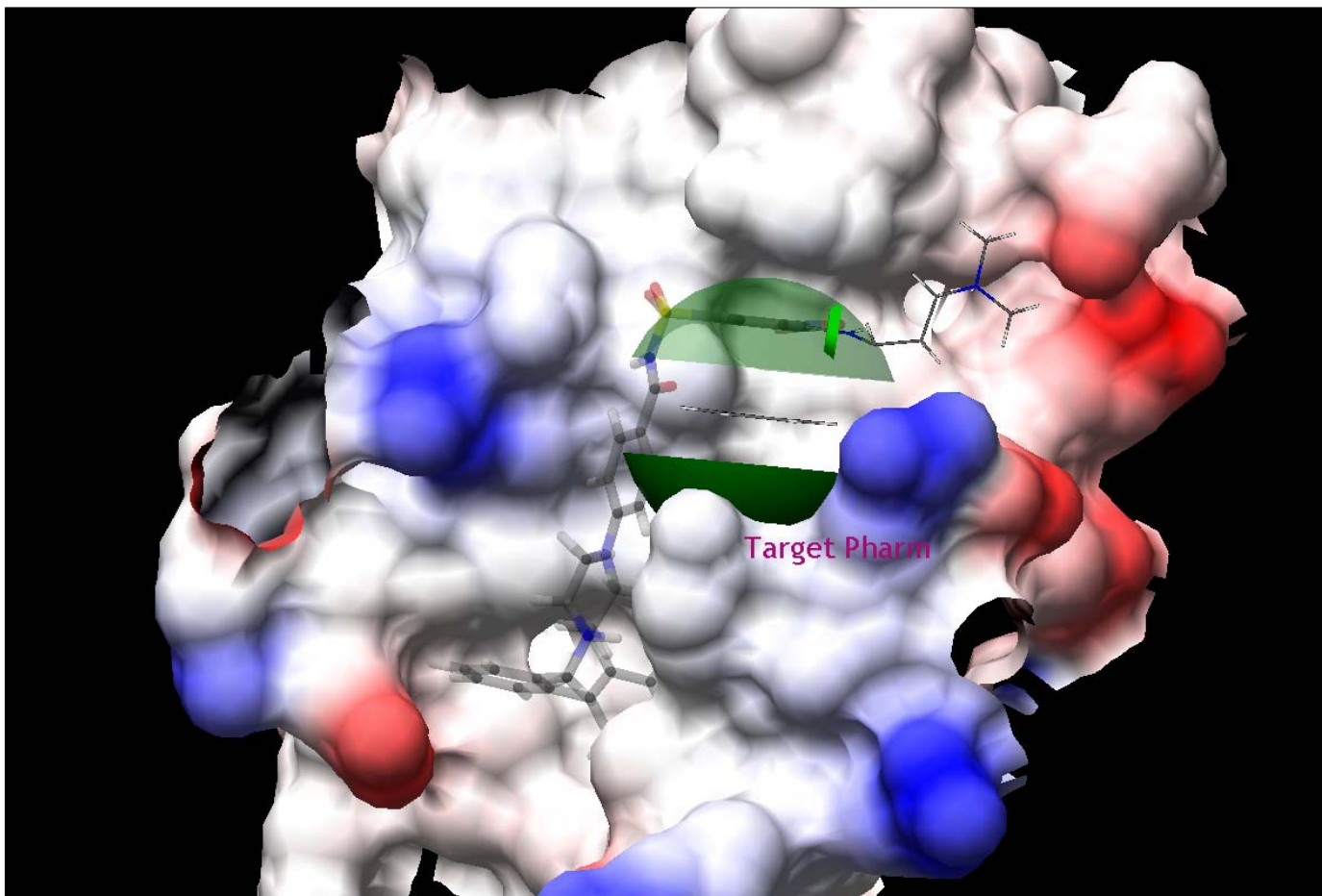
2 vectors are needed for the Query:

- Exit Vector
- π -interaction 'Pharm. Feature'



Growing into a π - π Interaction Pattern

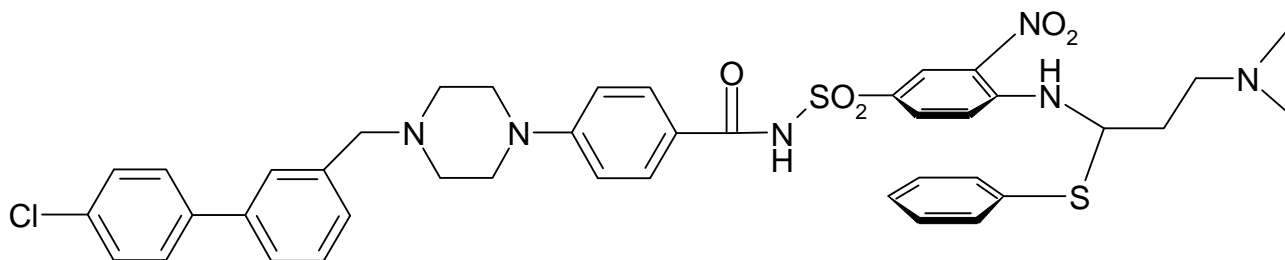
Here it is in 3D:



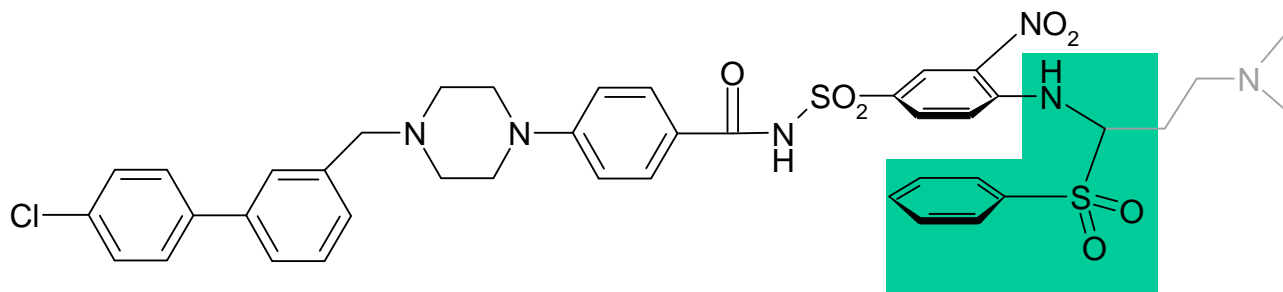
Growing into a π - π Interaction Pattern

The Result in 2D:

ABT-737

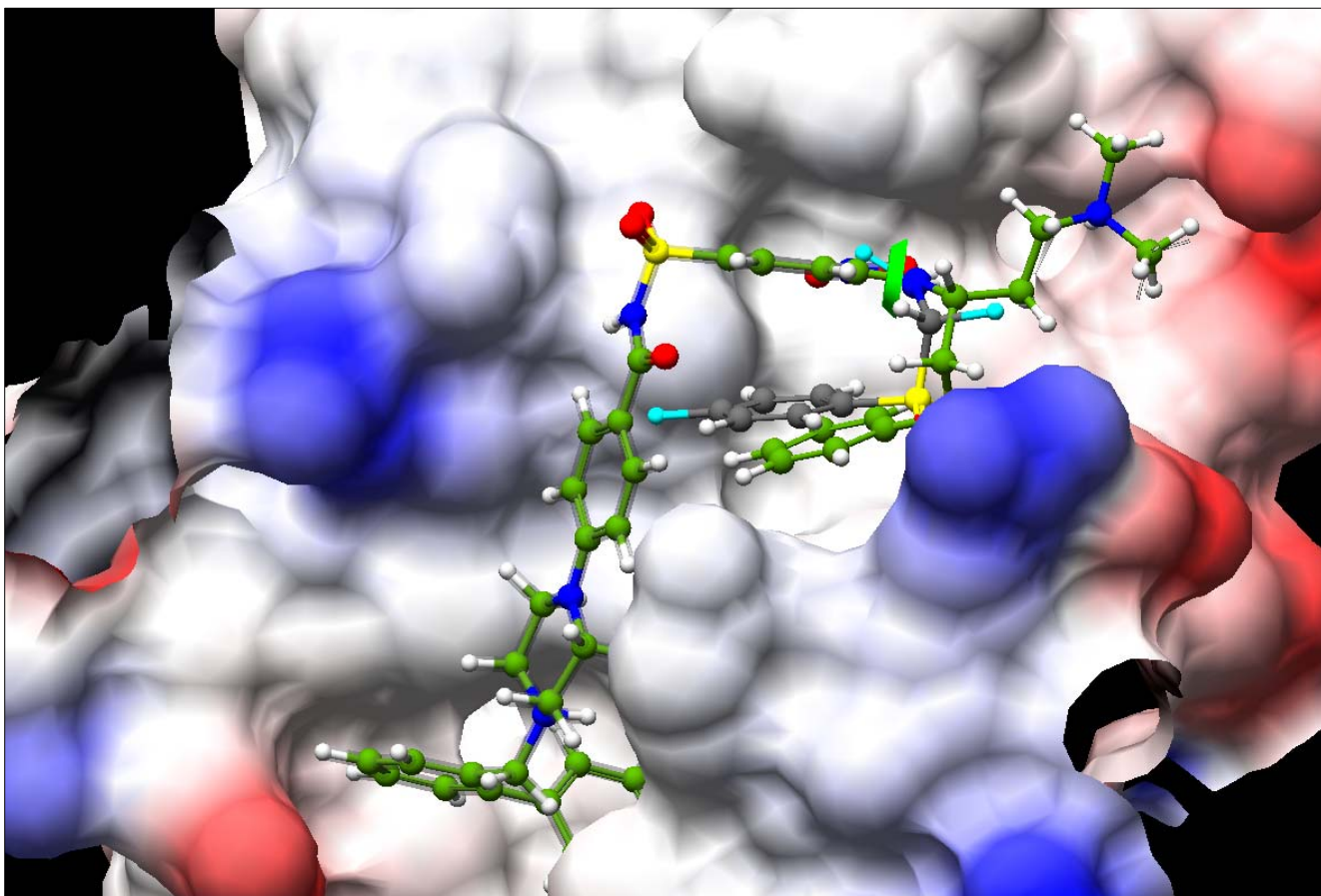


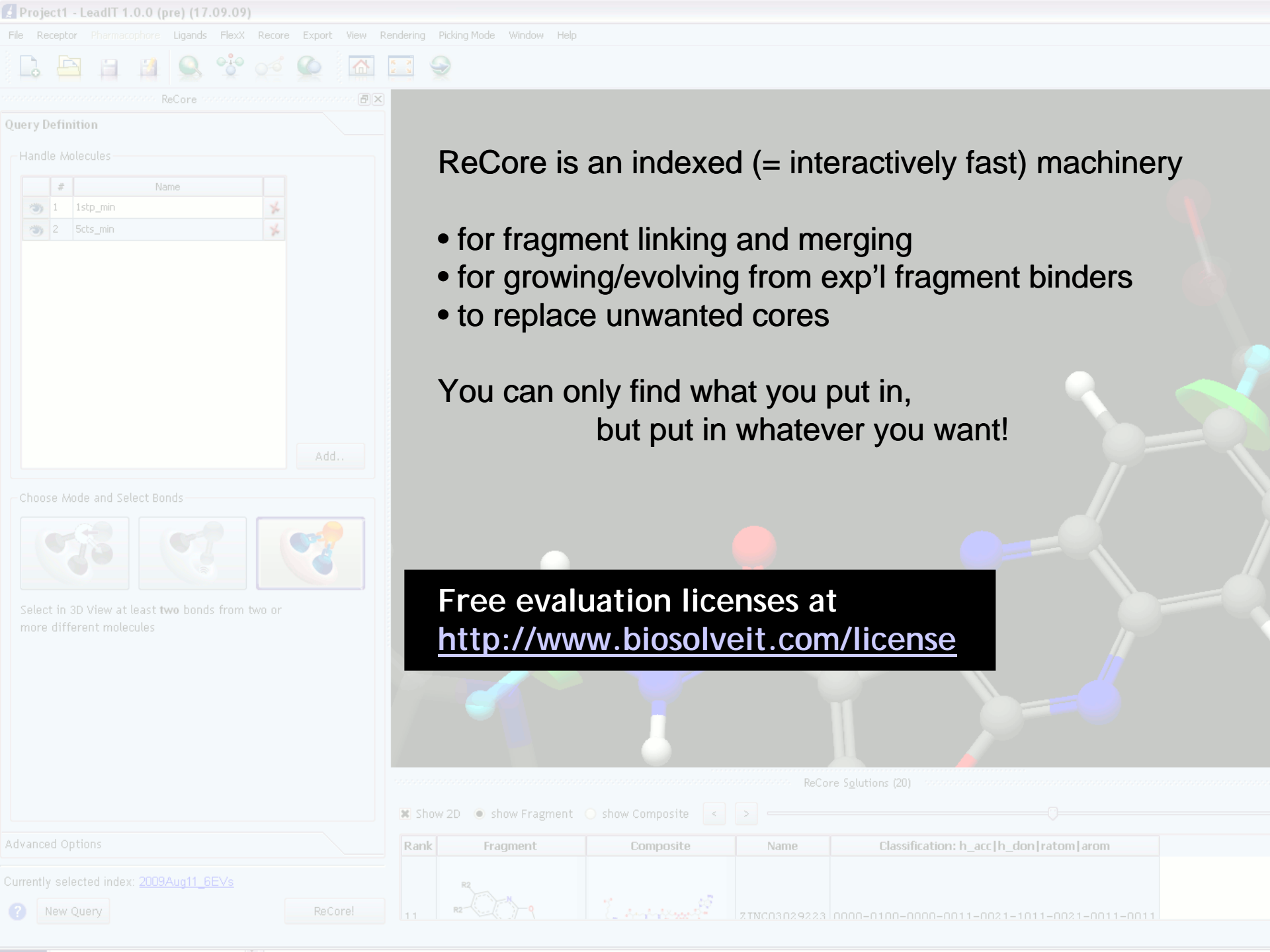
ReCore Solution No.11:



Growing into a π - π Interaction Pattern

Solution No. 11 in comparison to ABT-737 (green):
Almost identical positions obtained!





ReCore is an indexed (= interactively fast) machinery

- for fragment linking and merging
- for growing/evolving from exp'l fragment binders
- to replace unwanted cores

You can only find what you put in,
but put in whatever you want!

Free evaluation licenses at
<http://www.biosolveit.com/license>

ReCore Solutions (20)

Show 2D show Fragment show Composite

Rank	Fragment	Composite	Name	Classification: h_acc h_don ratom arom
11			ZINC03029223	0000-0100-0000-0011-0021-1011-0021-0011-0011